PSORIASIS: FROM GENE TO CLINIC CONGRESS REPORT

International conference showcases cutting-edge psoriasis research

By Dr. Satveer K. Mahil

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Psoriasis research is a leading example of translational research, in which basic science discoveries have informed the design and implementation of novel therapeutic approaches. Since its first meeting in 1996, Psoriasis: From Gene to Clinic has been a key international conference for showcasing cutting-edge psoriasis research. It brings together internationally renowned innovators in the field with an audience comprising clinicians, scientists and representatives from the pharmaceutical and biotechnology industries. The broad themes of the December 2014 meeting in London, United Kingdom, included genetics, immunology, comorbidities, and therapeutics. This article summarizes key topics discussed at the meeting.

Genetics

Professor Jonathan Barker, St John's Institute of Dermatology, United Kingdom, delivered a keynote lecture on the clinical utility of genetic observations in psoriasis and provided an overview of the cardinal genetic discoveries in the field, from the first identification of the association of PSORS-1 and HLA-Cw6 with psoriasis to more recent findings such as TYK2 risk alleles. Type 1 and type 2 disease (onset before and after age 40, respectively) are emerging as genetically distinct. Type 1 disease is more strongly associated with HLA-Cw6, and single nucleotide polymorphisms in IL-1B have been shown to specifically confer risk to type 2 disease.[1] Although most genetic variants that confer psoriasis susceptibility found to date have relatively small effect sizes, they provide important insights into the biology of the disease and have thus identified potential therapeutic targets. For example, genetic studies have highlighted the role of the Th17/IL-23 axis in psoriasis pathogenesis, and therapeutic agents such as ustekinumab have already successfully targeted components of this pathway.

Professor Barker also described the limitations of pharmacogenetic studies conducted to date, including small patient numbers and a lack of multidimensional analyses that account for confounders such as adherence to medications, body mass index (BMI), systemic comorbidities and inter-individual variation in pharmacokinetics. This will be addressed by the Psoriasis Stratification to Optimise Relevant Outcomes (PSORT) consortium (see therapeutics section). Despite the limitations, HLA-Cw6 has been shown to be associated with faster and greater response to ustekinumab in two recent studies.[2,3] These data support the implementation of careful stratification and integration of genetic data such as HLA typing in future clinical trials.

The complexities of combining multiple forms of data in large-scale studies – including information on genomics, transcriptomics, proteomics, metabolomics, and network analyses with rigorous statistical interpretation – were explored by Dr. Ewan Birney, Cambridge, United Kingdom. The importance of interdisciplinary teamwork, involving scientists, bioinformaticians and clinicians was emphasized.

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This will enable the progression of translational research and, specifically, the discovery and validation of drug targets. He described the transformation of the early stages of drug discovery, with academia now informing the pharmaceutical industry about reliable early-target discovery.

One study of generalized pustular psoriasis (GPP) provided an elegant example of how clinical features might be used to prioritize patients for mutation screening and therapeutic interventions, such as IL-1 receptor blockade.

Although researchers have made major advances through the discovery of more than 40 genetic loci associated with psoriasis by genome-wide association studies (GWAS), this only accounts for approximately 25% of the heritability of psoriasis. The "missing heritability" may be partly attributable to low frequency/rare variants, epigenetic factors, and genetic interactions. Most alleles found to confer psoriasis susceptibility by GWAS are common; however, large-scale sequencing in the general population has confirmed that the majority of genetic variation is rare. Dr. Michael Simpson, King's College London, United Kingdom, explained how the psoriasis Exome Chip Project, a large-scale international collaborative effort spearheaded by IPC, is addressing this discrepancy by evaluating low-frequency and rare (in addition to common) protein coding variation associated with psoriasis.[4] He reported the results from the first phase of the analysis, which confirmed previously observed coding variation associations and found novel associations of protein-altering variation at established and novel genetic loci. Phase 2 of the study is currently ongoing, which seeks to detect associations of rare genetic variants with psoriasis susceptibility and explore potential causality.

Dr. Francesca Capon, King's College London, United Kingdom, reported the findings of a genotype-phenotype correlation study in generalized pustular psoriasis (GPP).[5] Patients with GPP present with acute episodes of generalized skin pustulation accompanied by systemic upset. A meta-analysis of multiple GPP case series (n=233) found that patients with recessive IL36RN alleles experienced earlier onset of symptoms, lower incidence of psoriasis vulgaris, and a higher risk of systemic inflammation than patients without IL36RN mutations. An allele dosage effect was found, such that patients with a single IL36RN allele had delayed onset of GPP symptoms compared with those harboring two disease-associated recessive alleles. This study was an elegant example of how clinical features might be used to prioritize patients for mutation screening and therapeutic interventions such as IL-1 receptor blockade.

Professor Ken Smith, Cambridge Institute for Medical Research, United Kingdom, gave an exciting example of the utility of genetic biomarkers in predicting long-term patient outcomes and guiding therapies from an early stage of immune-mediated disease. CD8+ T-cell expression profiling at presentation of 2 groups of patients with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis correlated with outcomes after a median follow-up of 6 years. The patients were indistinguishable clinically at presentation. Therefore, immune cell transcription signatures may be used for the early stratification of patients with immune-mediated diseases in order to rationalize therapies.

Phase 2 of the psoriasis Exome Chip project, spearheaded by IPC, seeks to detect associations of rare genetic variants with psoriasis susceptibility and explore potential causality.

Immunology

Professor Jens Schroeder, University of Kiel, Germany, reviewed the role of the epidermis in psoriasis pathophysiology. The skin forms a unique innate immune antimicrobial chemical barrier. Central to this function are

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keratinocyte-derived anti-microbial peptides (AMPs). The AMP repertoire in lesional psoriatic skin is very different from normal skin, with evidence of upregulation of AMPs such as psoriasin, human β-defensin-2 (hBD2) and calprotectin. This suggests unique AMP-inducers within lesional psoriatic epidermis. Several pro-inflammatory cytokines induce AMPs such as hBD-2, and microbiome analyses have revealed a dominant presence of corynebacterium, staphylococcus and streptococcus in the microflora of lesional psoriatic skin compared with healthy skin. Hence, future investigations will determine whether psoriasis-specific bacterial species exist and/or which specific microbes these AMPs are targeting. For now, the source of the putative psoriasis antigen remains to be determined.

Professor Michel Gilliet, University Hospital, Lausanne, Switzerland, described the early cellular events in psoriasis and focused on the role of AMPs in activating the plasmacytoid dendritic cell (pDC)-interferon (IFN) pathway. pDCs have been shown to initiate psoriasis in xenograft models. They may be activated by AMPs, which are induced by skin injury (eg, hBD2). pDCs may also be activated by self-nucleic acids that are released into the extracellular environment by dying cells, and subsequently complex with AMPs to trigger activation of toll-like receptor (TLR) 7 and TLR9. pDCs are potent producers of type I IFN, which activates T cells, DCs, NK cells and is a signature cytokine for psoriasis that promotes the formation of a hyperproliferative epidermis. AMPs may also represent an auto-antigen that activates pathogenic Th17 cells in psoriasis.

Professors James Krueger, Rockefeller University, United States, and Frank Nestle, St John's Institute of Dermatology, United Kingdom, gave comprehensive overviews of the intracellular signaling pathways that are now being therapeutically targeted in psoriasis. JAK/STAT signalling is involved in the activation and differentiation of T cell subsets and is regulated by numerous cytokines that are upregulated in psoriatic skin lesions, such as IFNγ and type I IFN. There are 4 members of the JAK family; JAK1, JAK2, JAK3 and TYK2. The novel JAK inhibitors that are currently being evaluated in clinical trials have varying efficacy for each of the JAKs, eg, tofacitinib (predominantly JAK1 and JAK3 inhibition) and baricitinib (predominantly JAK1 and JAK2 inhibition). These small molecules target the intracellular signal transduction pathways and have shown promising results in clinical trials (see therapeutics section, p. 20).

The role of neutrophils was also highlighted in several talks throughout the conference. Neutrophils are a rich source of IL-17A (in addition to Th17 cells), which is critical to the pathogenesis of psoriasis through regulation of keratinocyte activity. Dr. Kristian Reich, Dermatologikum, Hamburg, Germany, described how the potent IL-17A inhibitor, secukinumab, causes a rapid reduction in cutaneous neutrophils alongside the downregulation of keratinocyte-derived chemokines that are neutrophil chemoattractants (eg, CCL20 and CXCL1).[6] These changes occur in parallel to a reduction in PASI and histological improvement in keratinocyte abnormalities. Effects on T cells and CD11c+ DCs were found to be more delayed.

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Comorbidities

Professor Donal O'Shea, St Vincent's Hospital, Ireland, gave an engaging talk on comorbidities in psoriasis, describing the molecular link between psoriasis and both obesity and diabetes. Fat is an immune organ that is involved in the dynamic regulation of weight. Fat contains invariant natural killer T (iNKT) cells that release IL-10 and IL-4 and are regulated by GLP-1. It was observed that treating diabetic patients with psoriasis with GLP-1 improves itch and also psoriasis. This highlights a potential role for gut hormones in the regulation of cutaneous inflammation.

This lecture was complemented by a number of free communications, including a description by Dr. Jens Peter Andersen, Aarhus University, Denmark, of the induction of pro-inflammatory responses by dermal fibroblasts after stimulation with leptin.[7] Serum levels of leptin, an adipokine secreted by adipose tissue, are elevated in both obese

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individuals and psoriasis patients. Leptin was found to induce CXCL1 and IL-6 secretion from fibroblasts, which are chemotactic for neutrophils and T cells, respectively. Leptin also upregulates ICAM-1 expression in fibroblasts, which promotes immune cell chemotaxis. Thus, leptin-mediated fibroblast regulation was proposed as one of the potential links between psoriasis and obesity.

A study using multimodal cardiac imaging to characterize the effect of psoriasis on cardiovascular disease showed greater evidence of *in vivo* vascular inflammation in psoriasis patients than controls, as well as reduced aortic arch wall distensibility.

Patients with psoriasis have an increased risk of cardiovascular disease, and psoriasis inflammation has been shown to accelerate atherosclerosis. Dr. Nehal N. Mehta, National Institutes of Health, United States, described the role of multimodal cardiac imaging in characterizing the effect of psoriasis on cardiovascular disease.[8] Seventy-five psoriasis patients and 16 control subjects were enrolled in the study; all subjects were at low risk for cardiovascular disease, according to the Framingham Risk Score. FDG Position Emission Tomography-Computed Tomography (PET/CT), FDG PET-Magnetic Resonance Imaging (MRI) and coronary CT angiography (CCTA) imaging modalities were used.

There was greater PET/MRI evidence of *in vivo* vascular inflammation in psoriasis patients than controls, as well as reduced aortic arch wall distensibility. CCTA showed greater total atherosclerotic plaque burden and non-calcified (macrophage-rich) plaque burden in psoriasis patients compared with either controls or subjects with known coronary artery disease. Hence, multimodal imaging demonstrated significant levels of inflammatory atherogenesis in psoriasis patients.

Dr. William Swindell, University of Michigan, United States, described an investigation into the biological basis of the association between atherosclerosis and psoriasis.[9] Transcriptome analysis of both psoriatic skin and carotid atherosclerotic plaque samples showed enrichment of tumor necrosis factor α (TNF-α) and IFNγ responsive genes. There was a 70% overlap between gene expression in psoriatic skin and atherosclerotic plaques, suggesting common cytokine and cellular responses and offering novel mechanistic insights into how cutaneous inflammation may accelerate atherosclerosis.

Professor Amy Paller, Northwestern University, United States, gave an informative talk on the comorbidities associated with childhood psoriasis, which represents 4% of all of the dermatoses in children. Psoriatic arthritis is less common and Crohn's disease more prevalent (4-fold) in children than adults with psoriasis. Psoriasis in childhood is recognized to have a profound effect on quality of life, with more affected children having a concurrent psychiatric disorder such as anxiety and depression than children without psoriasis. Metabolic disease is also associated with childhood psoriasis; there is increased risk of obesity in patients with psoriasis and increased risk of psoriasis among overweight children. A recent study suggested that excess adiposity precedes the onset of psoriasis and that those with a family history of obesity develop psoriasis at an earlier age.[10] Thus, young patients and their families should be counseled at an early stage regarding comorbidities and encouraged to adopt a healthy lifestyle. Clinicians should also record BMI and waist circumference routinely in children with psoriasis and consider monitoring fasting lipids and glucose in patients who are overweight/obese.

Metabolic disease is also associated with childhood psoriasis; there is increased risk of obesity in patients with psoriasis and increased risk of psoriasis among overweight children.

Therapeutics

Professor Gertjan Wolbrink, University of Amsterdam, Netherlands, described the pharmacological assessment of outcomes to biologic therapy. He proposed two major

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Given the major psychosocial morbidity associated with psoriasis, the adoption of a holistic approach when assessing and treating patients is essential.

reasons why some patients fail on TNF antagonist therapies. Firstly, patients may have sub-therapeutic serum drug levels due to an immunogenic response (anti-drug antibodies) against the drug. Secondly, TNF may not be the major cytokine driving the patient's disease, such that even effective blockade by adequate drug levels would not impact the course of the disease.

The considerable inter-individual variation in TNF antagonist drug levels in patients may be attributable to the extent to which anti-drug antibodies are formed. It has been shown that drug levels of biologics, such as adalimumab, correlate with response rates. It is favorable to measure drug levels in patients as opposed to anti-drug antibody levels due to several limitations of commonly used anti-drug antibody assays, including the inability to quantify total antibody levels (only free antibody is measured). A key focus for future research in this area is the regulation of the immune response to the drug, ie, the production of anti-drug antibodies, as this determines the serum drug level. Modulation of this immune response, possibly by altering co-medications and treatment schedules/doses may help to optimize serum drug levels in patients and hence improve therapeutic efficacy.

Professor Krueger of Rockefeller University reported the rapid clinical effects of tofacitinib (10 mg twice daily), an oral JAK inhibitor.[11] Decreased pruritus was observed after 1 day and greater numbers of patients achieved PASI 75 within 4 weeks relative to placebo. A serial skin biopsy-based study was performed to elucidate the mechanisms by which these clinical effects are achieved. Patient numbers were limited (n=9); however, there was evidence of reduced keratinocyte proliferation from day 1 of therapy in addition to decreased keratinocyte expression of phosphoSTAT1 and phosphoSTAT3 (drivers of keratinocyte hyperproliferation). Decreased CD11c+ myeloid DCs and IL-12B were expressed early on, and decreased T cells and IFNγ later. A successful response to tofacitinib was also associated with attenuation of the IL-23/Th17 axis, which regulates epidermal hyperplasia in psoriasis. Hence, the study suggests that there is a rapid inhibition of JAK/STAT signalling in keratinocytes early on during tofacitinib therapy, which reduces keratinocyte hyperplasia. This may lead to impaired cytokine-mediated inflammatory pathways, including IL-17, and reduced numbers of pathogenic inflammatory cells in the skin.

Professor Kim Papp, University of Western Ontario, Canada, reported the results of the phase 3 randomized, double-blinded, placebo-controlled trial of brodalumab in patients with psoriasis.[12] Brodalumab is a monoclonal antibody against the IL-17 receptor, which prevents binding to multiple IL-17 effectors. Those treated with brodalumab showed evidence of clinical response as early as 2 weeks. A higher proportion of brodalumab-treated patients achieved PASI 75 at 12 weeks (primary outcome measure) and also PASI 90 at 12 weeks. Patients were monitored for 1 year and most retained their response, without significant differences in adverse event rates between placebo and treatment arms.

UPDATE: After this article was written, Amgen stopped development of brodalumab "based on events of suicidal ideation in the brodalumab program," according to a company statement.

The considerable inter-individual variation in TNF antagonist drug levels in patients may be attributable to the extent to which anti-drug antibodies are formed.

Professor Chris Griffiths, University of Manchester, United Kingdom, described the current challenges facing psoriasis therapeutics. Given the major psychosocial morbidity associated with psoriasis, the adoption of a holistic approach when assessing and treating patients is essential. Psychological and quality of life outcome measures may not be accurately captured in the dermatology life quality index (DLQI). Patient-reported outcomes should be considered when assessing the effectiveness of new therapeutics. In addition, the clinical gold standard measure of treatment

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goal, PASI 75, was discussed, and PASI 90 proposed as a new target. Professor Griffiths explained that psoriasis is a very stratifiable disease and particularly suited to targeted therapies. The PSORT consortium, which integrates academia and industry, aims to determine and validate novel clinical, genetic and immune biomarkers in the skin and blood.[13] An exciting outcome of the project, which seeks to identify signatures of treatment response for psoriasis, is that patients may be placed on the correct biologic agent from the beginning of their treatment.

The clinical gold standard measure of treatment goal, PASI 75, was discussed, and PASI 90 proposed as a new target. Professor (Christopher) Griffiths explained that psoriasis is a very stratifiable disease and particularly suited to targeted therapies.

This talk was complemented by the invited lecturer on stratified medicine, Professor Stephen Holgate, University of Southampton, United Kingdom. He emphasized the need to integrate "omics" technology (genomics, epigenomics, transcriptomics, proteomics, metabolomics) with high-resolution phenotype information using statistical/bioinformatics approaches in order to achieve molecular phenotyping for guiding therapies for complex diseases. This represents a shift from descriptive pathology to molecular pathology, with novel molecular targets identified for directed therapies. Important lessons can be learned about stratified medicine approaches from oncology, in which causal mutation identification has revolutionized the targeted treatment of specific cancers, for example, herceptin for HER2+ breast cancer and imatinib for Philadelphia chromosome positive chronic myeloid leukemia. Thus the development of pathway-specific approaches, in which causal disease pathways are defined and effective treatments are designed for specific endotypes, is an imminent challenge in the treatment of psoriasis. It will require close collaboration and the effective integration of data across multiple disciplines such as molecular biology and bioinformatics. ■

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